IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Fox	Art Unit:	1731
Serial No.:	10/045,235	Examiner:	D. Walls
Filing Date:	October 29, 2001		
Title:	Device and Method for the Cessation of Smoking		

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

CERTIFICATION UNDER 37 C.F.R. § 1.8(a)

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on the date shown below.

August 1, 2003
Date of signature and of mail deposit

Maureen DiVito
Maureen DiVito

DECLARATION OF BARBARA S. FOX, PH.D. UNDER 37 C.F.R. § 1.132

Dear Sir:

I, Barbara S. Fox, Ph.D. declare as follows:

1. I am currently President and Chief Scientific Officer of Recovery Pharmaceuticals in Wayland, Massachusetts, which is the assignee of the above-referenced patent application ("the Application"). I have worked in the fields of bioscience research and drug development since obtaining my Ph.D. in biochemistry in 1983. My professional experience, educational background, professional activities, and publications are detailed in the *curriculum vitae* attached hereto as Exhibit A.

2. As the inventor, I have personal knowledge of the invention disclosed and claimed in the Application.

3. It has been brought to my attention that in the Office Action mailed on May 7, 2003, the Examiner rejected claims 1-9 and 13-15 under 35 U.S.C. § 103(a) as being obvious over Wong et al., U.S. Patent No. 6,106,845 in view of Ruecroft et al., U.S. Patent No. 5,663,356 ("Ruecroft"). The Examiner also rejected claims 10-12 and 16-41 under 35 U.S.C. § 103(a) as being obvious over Wong in view of Ruecroft, and further in view of Westman et al., U.S. Patent No. 6,211,194 ("Westman").

4. My understanding of the cited references is that Wong discloses an oral active agent delivery system for delivering discrete units of an active agent formulation to a patient, but does not teach or suggest that the active agent is nicotine. Ruecroft teaches that nicotine has been proposed to have a number of pharmacological effects, and reportedly potentiates the pharmacological behavior of certain pharmaceutical compositions used to treat central nervous system disorders. Westman discloses a solution containing nicotine.

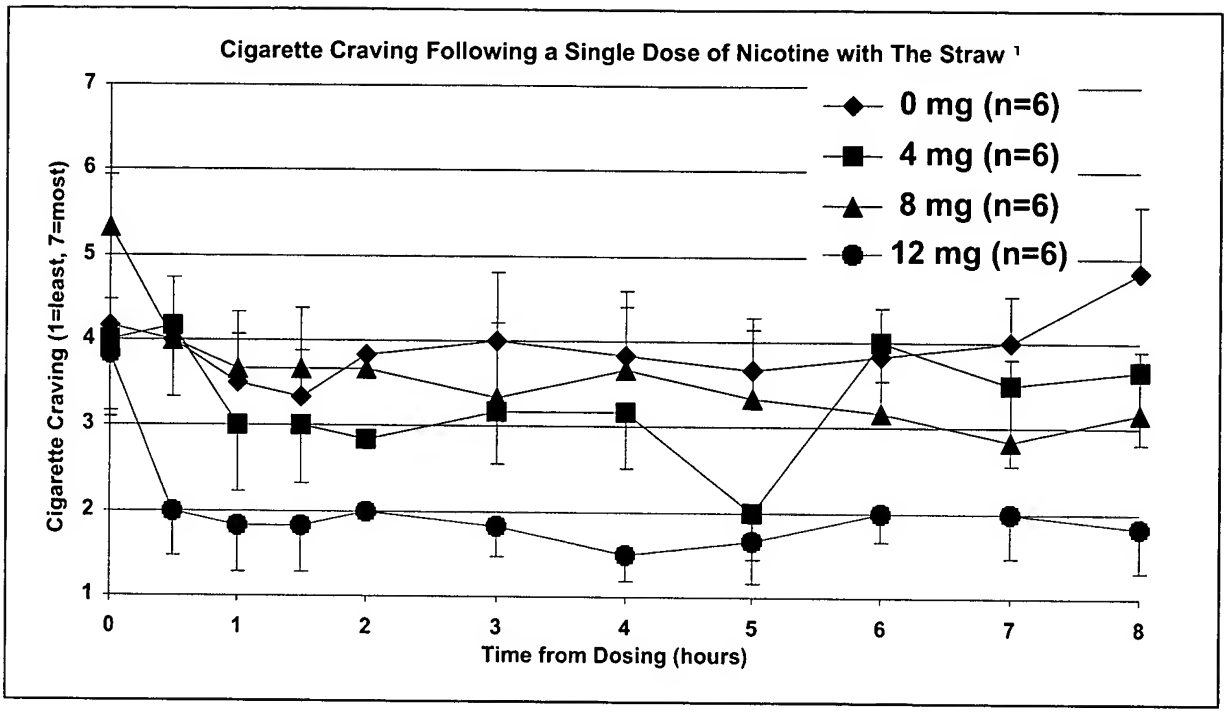
5. The devices and methods claimed in the Application provide unexpected synergistic results beyond what would be expected from combining the teachings of the prior art. In particular, the data presented below demonstrate that a device and method as claimed provide for a synergistic improvement in reducing smokers' cravings for cigarettes. The data indicate that a device and method as claimed reduced cigarette cravings more than would be expected by adding the craving reduction produced by the nicotine alone to the craving reduction produced by the same device without nicotine. This synergistically improved ability to reduce cigarette cravings promotes the effectiveness of the claimed devices and methods as smoking cessation aids.

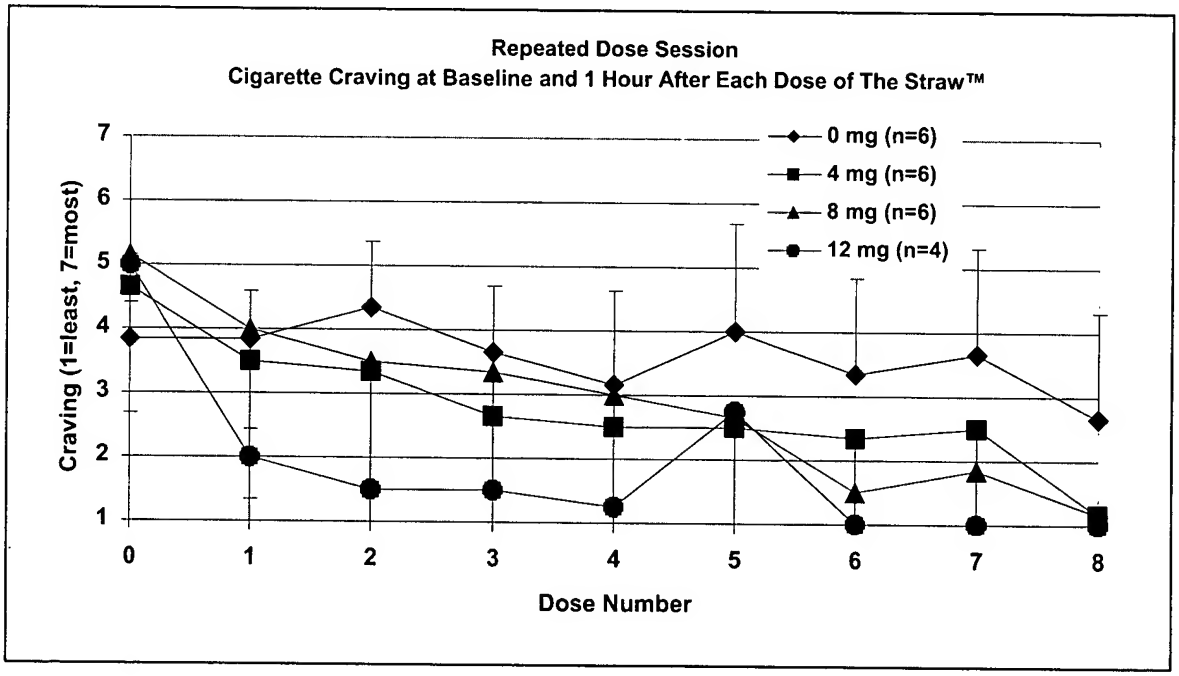
6. A clinical study was conducted with The Straw™ Nicotine Oral Delivery System, a nicotine delivery device as illustrated in Figure 1 of the Application. The Straw™ resembles a drinking straw containing a nicotine granulate. After removing the end cap at one end of the straw, a patient places the other end of the straw in a liquid, for example, juice. The end of the straw that is placed in the liquid has a retainer that allows liquid to pass through it, but prevents the nicotine from falling out that end of the straw. The patient sucks on the free end of the straw to draw the liquid and nicotine granulate into his mouth.

7. A clinical study of The Straw™ was conducted in 24 human subjects who smoked at least 10 cigarettes per day. Subjects abstained from smoking the night before the study. Subjects received 0 mg, 4 mg, 8 mg, or 12 mg nicotine per straw. In Part A of the study,

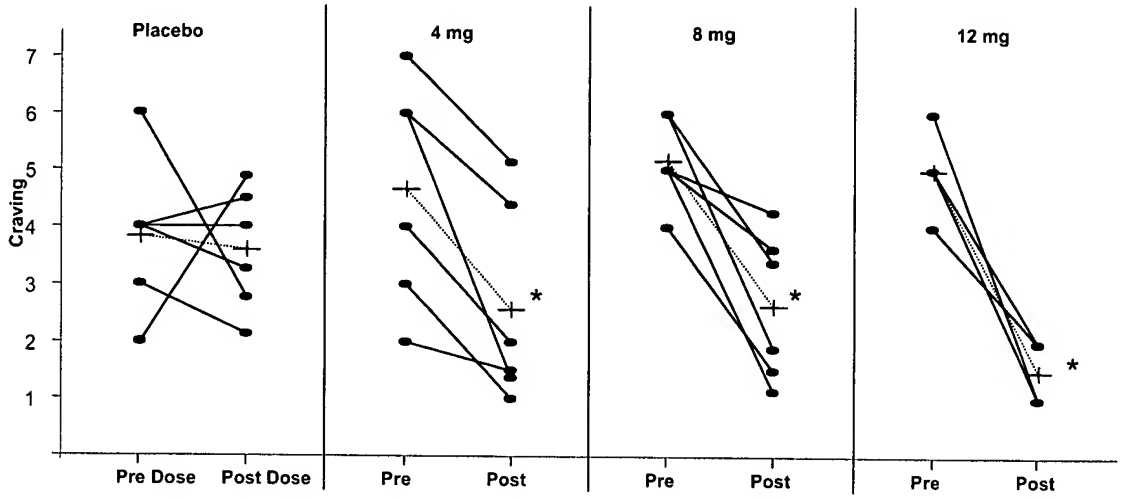
subjects received a single dose of nicotine with The Straw™, and blood samples, vital signs, adverse events, and cigarette craving data were collected frequently for 8 hours following dosing. The same subjects returned to the clinic one week later for Part B of the study. Subjects were assigned to the same unit dose they had received in Part A, and the same procedures were generally followed. Subjects received a dose of nicotine in The Straw™ every 1.5 hours over 10.5 hours for a total of 8 doses (0, 32, 64, or 96 mg nicotine total). Blood samples, vital signs, adverse events, and cigarette craving data were collected approximately 15 minutes prior to the first dose, and then one hour after each dose.

8. Cigarette craving was assessed at various times throughout the day following a single dose, and one hour after every dose during repeated dosing. Craving was evaluated using a question taken from the Shiffman-Jarvik Cigarette Smoking Withdrawal Questionnaire, "Have you craved cigarettes?" Craving was rated on scale of 1-7, with 7 being the most craving. Most subjects displayed moderate craving for cigarettes prior to dosing. Following a single dose, near the time of peak levels of nicotine (1.5 hour time point), craving had dropped from baseline by a mean (standard deviation) of 1.0 (1.0), 1.7 (1.0), and 2.0 (2.0) points for the 4, 8, and 12 mg nicotine groups, respectively, compared to only 0.8 (1.0) point in the placebo group, although the change from baseline was not statistically different among the groups (one-way ANOVA, $p=0.5$). Over the course of the repeated dosing session, craving scores decreased in all subjects in the nicotine groups. The mean (standard deviation) decrease was 2.1 (1.4), 2.5 (1.3), and 3.5 (1.2) points for the 4, 8, and 12 mg nicotine dose groups, respectively, compared to 0.25 (2.0) point for placebo ($p=0.02$, one-way ANOVA). The post-dosing data point for each individual was the mean value of the 8 assessments taken (one hour after each dose). In general, craving decreased continuously over the 10.5 hour repeated dosing session in the nicotine groups. Subjects receiving placebo straws exhibited a mixed response, with the net effect across the group being no change in craving. The following charts present the craving data for the single dose and repeated dose sessions.


Cigarette Craving Following a Single Dose of Nicotine with The Straw 1
Cigarette Craving (1=least, 7=most)
Time from Dosing (hours)
0 mg (n=6)
4 mg (n=6)
8 mg (n=6)
12 mg (n=6)


Repeated Dose Session
Cigarette Craving at Baseline and 1 Hour After Each Dose of The Straw™
Craving (1=least, 7=most)
Dose Number
0 mg (n=6)
4 mg (n=6)
8 mg (n=6)
12 mg (n=4)

The chart below presents individual and mean values of cigarette craving prior to and during the repeated dosing session with 0, 4, 8 or 12 mg nicotine via The Straw™.



Individual data are shown with solid lines. The data from all time points post-dosing for each individual have been collapsed into one data point. Mean values for each dose group are shown with dotted lines. * = $p \leq 0.01$, post-dose mean craving value statistically different from pre-dose craving value.

9. The above data demonstrate that The Straw™ reduces craving for cigarettes. The demonstrated effect in reducing craving was beyond that which would have been expected from adding the effect of the nicotine to the effect of the straw delivery device alone. The effect of the straw delivery device alone, in the absence of nicotine, is indicated by the placebo (0 mg nicotine) group in the above-described study. The effect of nicotine alone on cigarette craving has been studied by Hurt et al., Psychopharmacology **140**:98-104 (1998) (copy attached as Exhibit B). In that study, the investigators demonstrated that 4 mg nicotine gum, which delivers nicotine at a dose and with a kinetic profile similar to The Straw™, did not reduce cigarette craving beyond that seen with a placebo gum. In that study, subjects were dosed with the nicotine gum 3 times over 6 hours, roughly comparable to the first half of the repeated dosing section of the above-described study of The Straw™.

10. Thus, the combination of nicotine with the straw delivery device would not be expected to reduce cravings to a greater extent than the placebo device. In contrast, the data presented above show a statistically significant improvement in ability to reduce cravings by the nicotine-containing straw compared to placebo.

11. In conclusion, the above data and discussion demonstrate that the devices and methods claimed in the Application provide unexpected results beyond what would be expected from combining the teachings of the prior art. Specifically, the claimed devices and methods provide an unexpected synergistic improvement in reducing smokers' cravings for cigarettes, which promotes the effectiveness of the claimed devices and methods as smoking cessation aids.

I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Signed: Barbara S. Fox

Barbara S. Fox, Ph.D.

Dated: 7-31-03

6/10/2003

Barbara S. Fox, Ph.D.

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Career Profile

Successful scientist, innovator, executive and entrepreneur with significant achievements in bioscience research and drug development. Scientific expertise spans immunology, biochemistry, and neuroscience. Proven track record of advancing basic research findings into clinical development. Capabilities and agility as a leader demonstrated in both start-up and established companies. Inventor on 7 patents and patent applications and author of 39 publications.

Professional Experience

Chief Scientific Officer **1998 – date**
Founder, President
RECOVERY PHARMACEUTICALS, Wayland, MA

Founder, President and Chief Scientific Officer of Recovery Pharmaceuticals, a specialty pharmaceutical company developing medications for the treatment of patients with addictive disorders. Developed business concept, in-licensed founding technology, recruited world-class scientific advisory board, built management team, filed 4 patent applications and developed 3 products:

- Small molecule therapeutic for cocaine addiction (Cobrex™). Negotiated technology license from Research Triangle Institute, raised $4.7 million in NIH funding, moved product into late-stage pre-clinical toxicology testing.
- Novel form of nicotine replacement therapy for smoking cessation (The Straw™). Invented product concept, negotiated technology license from Duke, brought product through successful Phase I/II clinical trial.
- Specialty multivitamin for alcoholics (ThiaSure™). Developed product concept, brought product to market.

IMMULOGIC PHARMACEUTICAL CORP., Waltham, MA **1993 – 1998**

Vice President, Immunology 1996 – 1998

Head of Research Department. Led group of 25 scientists in basic research, pre-clinical product development and Bioassay. Responsible for work in areas of human and animal immunology, vaccine development, allergy, autoimmune disease, and substance abuse. Supported clinical programs, efforts to sell and partner company's technology.

Vice President, Discovery Research 1994 - 1996

Led research on two early stage programs, directing all research efforts and responsible for all external presentations. Managed termination of one program and advancement of cocaine vaccine program from Discovery into pre-clinical development.

Project Leader, Cocaine Vaccine Program 1995 – 1998

Led development of cocaine vaccine from Discovery into Phase I clinical trial. Responsible for direction of all activities necessary for development of protein conjugate cocaine vaccine, including process development, formulation, manufacturing, toxicology and development of the clinical operating plan. Vaccine is currently in Phase II clinical trials at Xenova.

Senior Scientist, Discovery Research 1993

U. MARYLAND SCHOOL OF MEDICINE, Baltimore, MD 1987 – 1993

Associate Professor of Medicine with tenure 1993

Division of Rheumatology and Clinical Immunology

Assistant Professor of Medicine 1987 – 1993

Division of Rheumatology and Clinical Immunology
Adjunct Asst. Prof. Microbiology & Immunology, Biochemistry and Pathology

Basic research in T cell activation, cytokine regulation, and the effect of aging on immune regulation

Education

1974 - 1978	Bryn Mawr College A.B. in Chemistry
1979 - 1983	Massachusetts Institute of Technology Ph.D. in Biochemistry, Department of Chemistry MIT Chemistry Department Fellow (1979 - 1980) National Science Foundation Predoctoral Fellow (1980-1983) Research Supervisor: Dr. Christopher T. Walsh
1983 - 1987	National Institutes of Health Postdoctoral Fellow, Laboratory of Immunology Jane Coffin Childs Memorial Fund Postdoctoral Fellow (1983-1986) National Institutes of Health Postdoctoral Fellow (1986-1987) Research Supervisor: Dr. Ronald H. Schwartz

Professional Memberships

College on Problems of Drug Dependence
Society for Research on Nicotine and Tobacco
American Association for the Advancement of Science
American Society for Biochemistry & Molecular Biology

Review Panels

2002, 2003	Ad Hoc Member, NIDA Medication Development Research Subcommittee, NIDA, NIH
1999	Member, Special Emphasis Panel on cancer vaccines, NIDCR, NIH
1998	Member, Special Emphasis Panel, "Strategic Program for Innovative Research in Cocaine Addiction Pharmacotherapy," NIDA, NIH
1994 - 1996	Member, Cellular Immunology Study Section, Arthritis Foundation
1992 - 1996	Member, NIH AIDS and Related Research Study Section 4 (ARRD)
1994	Member, Special Review Committee, "Immunologic Enhancement of Vaccine Immunogenicity," NIAID, NIH
1991 - 1992	Special member, NIH AIDS and Related Research Study Section 4 (ARRD)

Major Grant Support

2000 – date	Novel Pharmacotherapy for Treatment of Cocaine Addiction SPIRCAP grant National Institute on Drug Abuse, NIH F. Ivy Carroll, Principal Investigator
1997 - 1998	Therapeutic Cocaine Vaccine SPIRCAP grant National Institute on Drug Abuse, NIH Barbara S. Fox, Principal Investigator (resigned as PI upon leaving ImmuLogic)
1996 - 1998	Antibody Intervention in Cocaine Addiction Phase II SBIR grant National Institute on Drug Abuse, NIH Barbara S. Fox, Principal Investigator
1993	Th0 Cell Signalling Pathways for IL-2 & IL-4 Production NIH R01 AI33448 Barbara S. Fox, Principal Investigator Awarded 1993-1996, turned back after moving to ImmuLogic
1992 - 1993	Cell-associated costimulatory signal for IL-4 production Maryland Arthritis Foundation Barbara S. Fox, Principal Investigator
1989 - 1992	Effect of adjuvants on murine helper T cells NIH U01 AI28718 Barbara S. Fox, Principal Investigator
1988 - 1993	Influence of immunization regimen on helper T cells NIH R29 CA48664 Barbara S. Fox, Principal Investigator

Publications

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2. Fox, B.S. and C.T. Walsh. Mercuric Reductase: Homology to glutathione reductase and lipoamide dehydrogenase. Iodoacetamide alkylation and sequence of the active site peptide. Biochemistry 22:4082-4088, 1983.

3. Fox, B. and C. Walsh. Studies on bacterial mercuric ion reductase. In Mech. Drug Action, [Proc. Symp. Biochem. Basis Drug Action]. (T.P. Singer, T.E. Mansour and R.N. Ondarza, eds.) Academic Press, Orlando, FL., 317-326, 1983.

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Psychopharmacology (1998) 140 : 98–104

ORIGINAL INVESTIGATION

R.D. Hurt · K.P. Offord · I.T. Croghan
G.A. Croghan · L.C. Gomez-Dahl · T.D. Wolter
L.C. Dale · T.P. Moyer

Temporal effects of nicotine nasal spray and gum on nicotine withdrawal symptoms

Received: 18 February 1998/Final version: 1 May 1998

Abstract Nicotine nasal spray and nicotine gum have been found to be effective in relieving nicotine withdrawal symptoms. In this randomized single-blind study, 91 cigarette smokers were randomly assigned to a single 1 mg dose of active nicotine nasal spray (n = 29), active 4 mg nicotine gum (n = 31), saline placebo nasal spray (n = 16) or placebo gum (n = 15). Following overnight abstinence, subjects repeatedly completed visual analog scales for assessing nicotine withdrawal symptoms over 30 min preceding (time -30 min to time 0) and 120 min following a single dose of study medication. This sequence was performed 3 times during the day. Nicotine withdrawal symptoms were assessed on a 41-point visual analog scale (1 = no withdrawal, 41 = extreme withdrawal). At the initial session only, blood samples for serum nicotine levels were taken at baseline, then at 5, 10, 30 and 120 min following study drug administration. The mean (± SD) age of the subjects was 38.6 (±10.1) years, 48% were females, smoking rate was 24.5 (±7.8) cigarettes per day, and years of smoking was 19.9 (±10.0). A single 1 mg dose of nicotine nasal spray provided more immediate relief for craving for a cigarette compared to a single 4 mg dose of nicotine gum. Serum venous nicotine levels for the active nicotine nasal spray and nicotine gum were comparable at 5 and 10 min while the levels were higher for nicotine gum at 30 and 120 min. Changes in withdrawal symptoms were not found to be related to serum venous nicotine levels. Our findings provide a rationale for the as needed use of nicotine nasal spray to control withdrawal symptoms, possibly in combination with other medications with longer acting effects.

Key words Nicotine gum · Nicotine nasal spray · Nicotine withdrawal symptom · Nicotine blood level

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Introduction

The efficacy of nicotine gum (Cepeda-Benito 1993) and nicotine nasal spray (Sutherland et al. 1992; Hjalmarson et al. 1994; Schneider et al. 1995) as aids to smoking cessation have been well established. Nicotine nasal spray appears to work better than placebo in more heavily dependent smokers, even though the blood nicotine levels are relatively low compared to those while smoking (Sutherland et al. 1992; Hjalmarson et al. 1994; Schneider et al. 1995; Hurt et al. 1998). Though a different nasal delivery system was used, repeated administration of a 1 mg intranasal dose of nicotine in separate sessions produced similar plasma nicotine levels (Pomerleau et al. 1992). A recent review compares nasal absorption of nicotine with various devices and to other nicotine delivery systems, and shows more rapid delivery with intranasal administration (Schneider et al. 1996). Higher transient levels of nicotine may be more effective in reducing urges to smoke (Henningfield et al. 1993).

A major difference between the various available nicotine replacement products is the rate of nicotine delivery resulting from the pharmacokinetic properties of the delivery system. Nicotine delivery is slowest

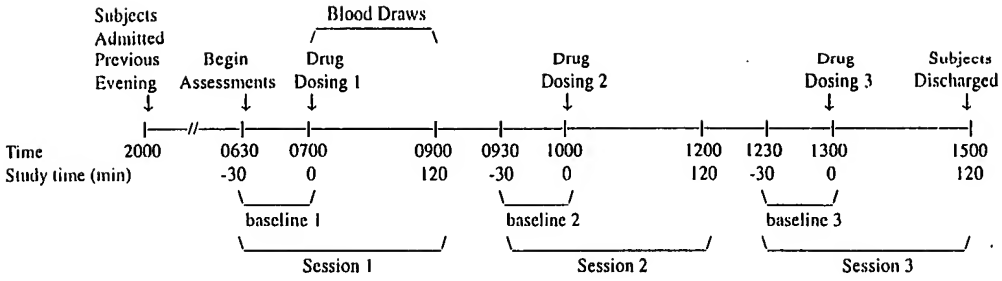

Fig. 1 The schema shows the timeline of events for this study. Withdrawal assessments were recorded every 5 min during baseline, every 5 min for the first 30 min following drug administration, and every 10 min thereafter for 2 h. Blood samples were obtained during the first session at times 0, 5, 10, 30 and 120 min

via the transdermal route (nicotine patch), taking 3–10 h to reach the peak level. Buccal absorption (nicotine gum) is somewhat faster, with peak nicotine concentration occurring after 30 min of initiating use (Russell et al. 1976). The fastest mode of nicotine replacement thus far is nasal mucosal absorption when delivered by nasal spray, which produces peak venous nicotine concentrations of 2–12 ng/ml in 4–15 min from a single 1 mg dose of nicotine. Furthermore, the arterial nicotine concentrations are higher than venous levels after a single 1 mg nicotine nasal spray dose, but the levels remain substantially lower than arterial levels achieved smoking a cigarette (Gourlay and Benowitz 1997). The sharp rise in blood nicotine and then gradual decline when delivered via cigarette smoke is a pattern thought to provide the unique reinforcing properties of cigarette smoking (Pomerleau and Pomerleau 1984).

There are no studies that directly compare the latency of the rise in serum nicotine concentration and the speed of craving and withdrawal symptom relief of nicotine gum and nicotine nasal spray. The present study attempts to examine the relationship between the pharmacokinetic properties and craving/nicotine withdrawal relief in smokers for these two fastest clinically available nicotine delivery systems. The study was approved by the Mayo Foundation Institutional Review Board.

Materials and methods

We recruited 91 cigarette smokers via press releases to stay overnight and throughout the 1 day study in a research unit. They were randomized to receive either active nicotine nasal spray, active 4 mg nicotine gum, placebo gum or saline placebo nasal spray the following morning while in this unit. At entry, subjects were screened for the inclusion/exclusion criteria. Inclusion criteria were: 18–65 years of age, smoked ≥15 cigarettes per day for the past year, good health verified by physical exam and laboratory testing and subject report of moderate or severe craving or urge to smoke a cigarette within 30 min of arising.

Exclusion criteria were: recent (within 6 months) myocardial infarction, angina pectoris, or other serious medical condition; active chemical dependence other than nicotine dependence; current psychiatric disorder; chronic nasal disorder (polyps, chronic nasal congestion, allergies, sinusitis); pregnant or lactating; weight <100 lb; current use of nicotine products other than cigarettes; any bridgework, temporomandibular joint dysfunction, dentures or any other condition which would preclude proper use of nicotine gum; any past or current use of nicotine gum or nicotine nasal spray; and finally, current use of clonidine, buspirone, doxepin, bupropion, fluoxetine or other psychotropic drugs.

After providing informed consent and completing a brief physical examination, qualified subjects were admitted to a research unit by 8:00 p.m. and were randomized to receive 1 mg nicotine dose (i.e., 0.5 mg per nostril) of the nicotine nasal spray (n = 29), saline placebo nasal spray (n = 16), 4 mg nicotine gum (n = 31), or placebo gum (n = 15). Subjects were housed in separate rooms and were not allowed to observe the medications that other subjects were administered. Following observed overnight abstinence from smoking, subjects were awakened at 6:00 a.m., whereupon they had breakfast. They were then instructed in the proper use of their assigned drug as well as other study procedures by a study assistant. Subjects assigned to the active or placebo gum were instructed to use it for 30 min. Figure 1 shows the timeline of events.

Subjects completed visual analog scales for assessing nicotine withdrawal symptoms beginning at 6:30 a.m. These were collected by a study assistant after completion by the subject. The investigators were not involved in the collection of these data, thus had little chance to be influenced by the medication assignment of the individual subjects. Withdrawal symptoms were assessed on a 41-point scale (1 = no withdrawal, 41 = extreme withdrawal) using the question, "Please indicate how much you are experiencing each sensation at this moment." The key measures of withdrawal were "craving for a cigarette and cigarette withdrawal." Other questions inquired about: How anxious? How irritable? How angry? How frustrated? How depressed? Ability to concentrate and degree of hunger. Measurements of withdrawal symptoms were recorded every 5 min for 30 min preceding study drug administration.

At 7:00 a.m., each subject received the first dose of their assigned medication, i.e. nicotine nasal spray, nicotine gum, placebo nasal spray or placebo gum. Following drug administration, withdrawal symptoms were recorded every 5 min for the first 30 min and then every 10 min thereafter through 2 h. In order to determine if withdrawal symptom relief would be consistent over three separate doses and times, the identical sequence of assessments and dosing was performed 3 times during the day, with a 30-min interval between sessions. Subjects were then dismissed from the research unit.

For the first session only, serum nicotine samples were taken 5 times; once at baseline and then at 5, 10, 30 and 120 min following drug administration. Blood samples for nicotine were not drawn during the subsequent two sessions because of the large amount of blood that would require, plus the concern that there could be accumulation of nicotine with subsequent doses. Serum nicotine concentrations were determined using gas chromatography and mass spectrometry (Baskin et al. 1998). The lower limit of accurate detection of this assay is 2.0 ng/ml; thus, levels below that are reported as undetectable. Our ability to assess changes from baseline nicotine levels was limited by the detection limit of the assay; therefore, we did not report mean levels on changes from baseline.

Data analysis

Baseline characteristics were assessed for comparability between the four treatment groups using analysis of variance for continuous and

Table 1 Baseline demographics

Characteristic	Overall (n = 91)	Active gum (n = 31)	Active spray (n = 29)	Placebo gum (n = 15)	Placebo spray (n = 16)
	n (%)	n (%)	n (%)	n (%)	n (%)
Gender					
Female	44 (48)	15 (48)	14 (48)	7 (47)	8 (50)
Male	47 (52)	16 (52)	15 (52)	8 (53)	8 (50)
Age (years)	38.6 ± 10.1	38.6 ± 9.7	38.3 ± 10.3	36.2 ± 10.9	41.3 ± 10.2
Smoking rate[a]	24.5 ± 7.8	23.0 ± 6.9	26.3 ± 7.9	22.7 ± 8.5	25.9 ± 8.6
Years of smoking	19.9 ± 10.0	19.6 ± 9.7	19.9 ± 9.9	18.3 ± 11.5	22.3 ± 9.8
Pack years[b]	26.2 ± 17.4	25.7 ± 16.9	27.3± 17.3	21.5 ± 18.7	29.6 ± 18.1
FTND[c]	10.1 ± 2.7	10.2 ± 4.1	10.2 ± 1.6	10.2 ± 1.4	9.8 ± 1.5

[a]Average cigarettes per day
[b]Average cigarettes per day divided by 20, multiplied by years of smoking
[c]Fagerström Test for Nicotine Dependence

Table 2 Serum nicotine levels, ng/ml. Entries are median; percentage of levels <2.0 ng/ml (the assay detection limit); and range of serum nicotine levels

Time[a]	Active gum (n = 31)			Active spray (n = 29)			Combined placebo (n = 31)			P-value[b]		
	Median	%	Range	Median	%	Range	Median	%	Range	AG vs. P	AS vs. P	AG vs. AS
0	3.0	36	<2.0–12.0	2.6	31	< 2.0–7.2	2.8	26	<2.0–12.5	NS	NS	NS
5	3.2	23	<2.0–12.6	4.9	17	<2.0–11.5	2.7	36	<2.0–8.1	NS	0.003	NS
10	3.7	26	<2.0–22.2	5.1	7	<2.0–11.0	2.7	39	<2.0–6.5	0.042	<0.001	NS
30	7.7	7	<2.0–22.4	4.7	10	<2.0–10.4	2.4	39	<2.0–7.6	<0.001	0.001	0.011
120	5.4	16	<2.0–16.9	3.2	24	<2.0–7.6	2.0	48	<2.0–7.6	<0.001	0.010	0.048

[a]Minutes following drug administration
[b]Rank Sum test comparing: active gum vs. combined placebo; active spray vs. combined placebo; and active gum vs. active spray

Fisher's exact test for categorical variables. Nicotine withdrawal symptoms were analyzed using a composite nicotine withdrawal score, computed as the mean of the nine withdrawal symptoms assessed and individually for symptoms "craving for a cigarette" and "cigarette withdrawal." The specific interest of analyzing the craving and cigarette withdrawal symptoms individually was identified a priori. Repeated measures analysis was used to determine time and session effects on the change from baseline in the composite nicotine withdrawal, craving for a cigarette, and cigarette withdrawal scores. After verifying that the effect of treatment was not dependent on session and that there were no session effects, these nicotine withdrawal symptoms were analyzed using the change in mean cumulative area under the withdrawal score against time-response curve, averaged across the three sessions. The comparisons of active gum versus active spray, active gum versus placebo gum, and active spray versus placebo spray were identified a priori to be of specific interest. Also, since both placebo groups received no active nicotine, we compared the two placebo groups and combined as appropriate. In particular, the serum nicotine analysis results were combined for the two placebo groups. Spearman's rank correlation analysis was used for the first study session to assess the association between serum nicotine levels and the change in withdrawal symptoms across treatment groups. Additional statistical methods included one-sample and two-sample t-tests, rank sum tests and repeated measures analysis of variance. In all cases, P-values ≤ 0.05 were used to denote statistical significance.

The most critical comparison was projected to be active nicotine nasal spray versus active nicotine gum. Hence, we randomized approximately 30 subjects to each of these two treatment groups (29 to nicotine nasal spray and 31 to nicotine gum). This provided power of > 0.90 of detecting group differences of 0.90 SD or larger (SD is within-group, between-subjects standard deviation for the change from baseline withdrawal symptoms) using a two-sided, $\alpha = 0.05$ test.

Results

Table 1 shows the demographics of the study subjects. The mean (± SD) age of the subjects was 38.6 (±10.1) years, 48% were females, smoking rate was 24.5 (±7.8) cigarettes per day, and the mean years of smoking was 19.9 (±10.0) years. No significant differences were observed among treatment groups for any of the baseline characteristics presented.

Table 2 shows the median venous serum nicotine levels for the active spray, active gum and the combined placebo arms. The median levels were used to avoid the potential for overestimation of the mean levels if 2.0 ng/ml was used for undetectable levels in the calculation of the mean. Nicotine gum (4 mg) and nicotine nasal spray (1 mg) were not found to have significant differences in nicotine levels at 5 and 10 min following a single dose, but nicotine gum provided higher nicotine levels at 30 min (median levels active gum: 7.7 ng/ml versus active spray: 4.7 ng/ml,

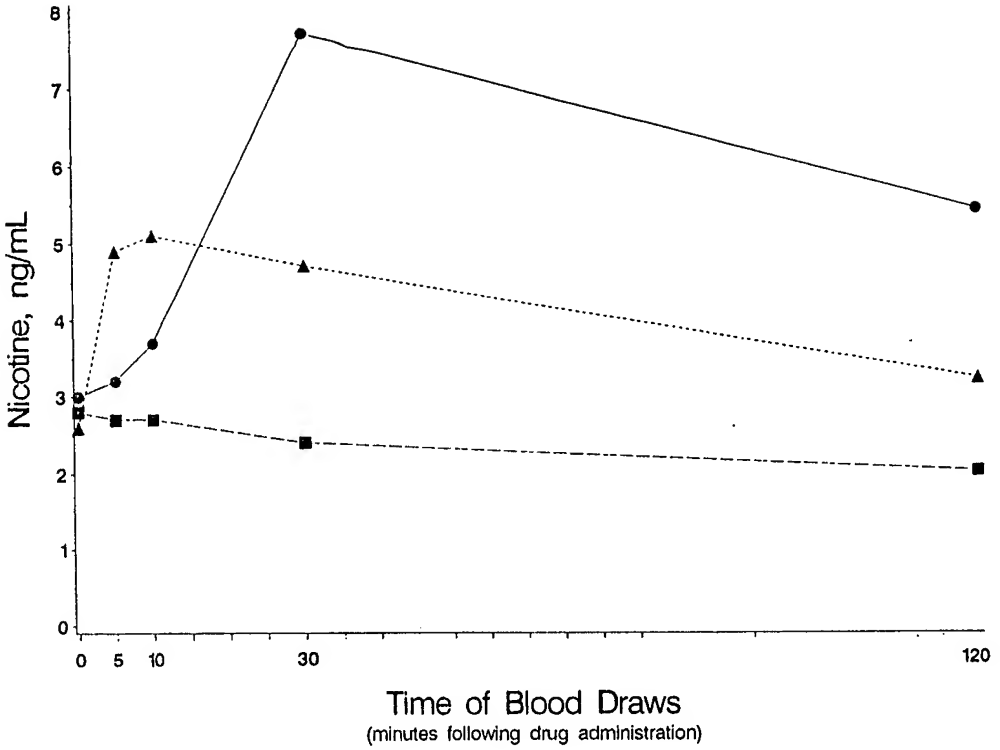

Fig. 2 Median serum nicotine levels (ng/ml) for the first study session according to study drug. The combined placebo group includes both the placebo gum ($n = 15$) and placebo spray ($n = 16$) groups. Serum nicotine levels for single doses of active nicotine gum (4 mg) and active nicotine nasal spray (1 mg) were not significantly different at 5 and 10 min, while the nicotine levels for the active gum were significantly higher than active spray at 30 and 120 min. Serum nicotine levels for active gum were significantly higher than combined placebo at 10, 30 and 120 min. Serum nicotine levels for active spray were significantly higher than combined placebo at 5, 10, 30 and 120 min. ○ 4 mg active gum ($n = 31$), ▲ 1 mg active spray ($n = 29$), ■ combined placebo ($n = 31$)

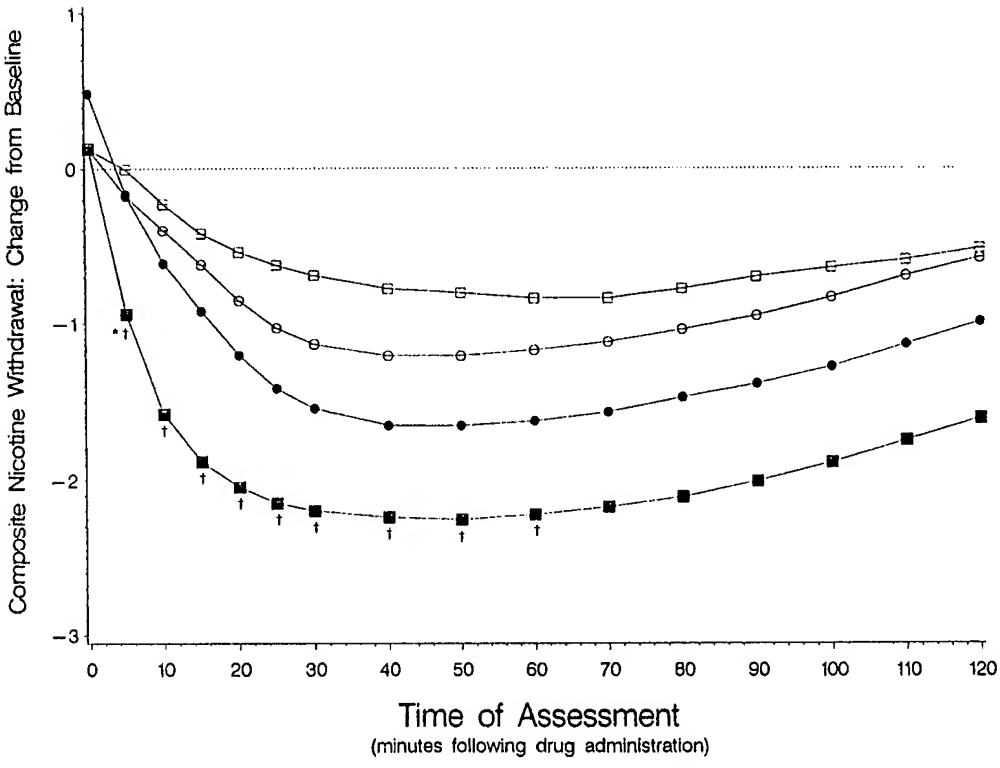

Fig. 3 Mean composite nicotine withdrawal change from baseline in cumulative area under the curve, averaged across all three study sessions. Composite nicotine withdrawal score computed as the average of the nine nicotine withdrawal symptoms, each based on a scale from 1 (no withdrawal) to 41 (extreme withdrawal). A larger negative value represents a larger reduction in overall nicotine withdrawal score. *$P < 0.05$ from two-sample t-test comparing active spray versus active gum. †$P < 0.05$ from two-sample t-test comparing active spray versus placebo spray. □ Placebo spray ($n = 16$), ○ placebo gum ($n = 15$), ○ 4 mg active gum ($n = 31$), ■ 1 mg active spray ($n = 29$)

$P = 0.011$) and 120 min (active gum: 5.4 ng/ml versus active spray: 3.2 ng/ml, $P = 0.048$). Nicotine levels for active gum were significantly higher than combined placebo at 10, 30 and 120 min, and nicotine levels for active spray were significantly higher than combined placebo at 5, 10, 30 and 120 min ($P < 0.05$ for all cases).

Figure 2 shows the median serum nicotine levels for the active nicotine nasal spray, active nicotine gum and the combined placebo groups.

Figure 3 shows the change from baseline (the 30 min prior to the drug administration) in composite nicotine withdrawal scores for the four groups. The AUC

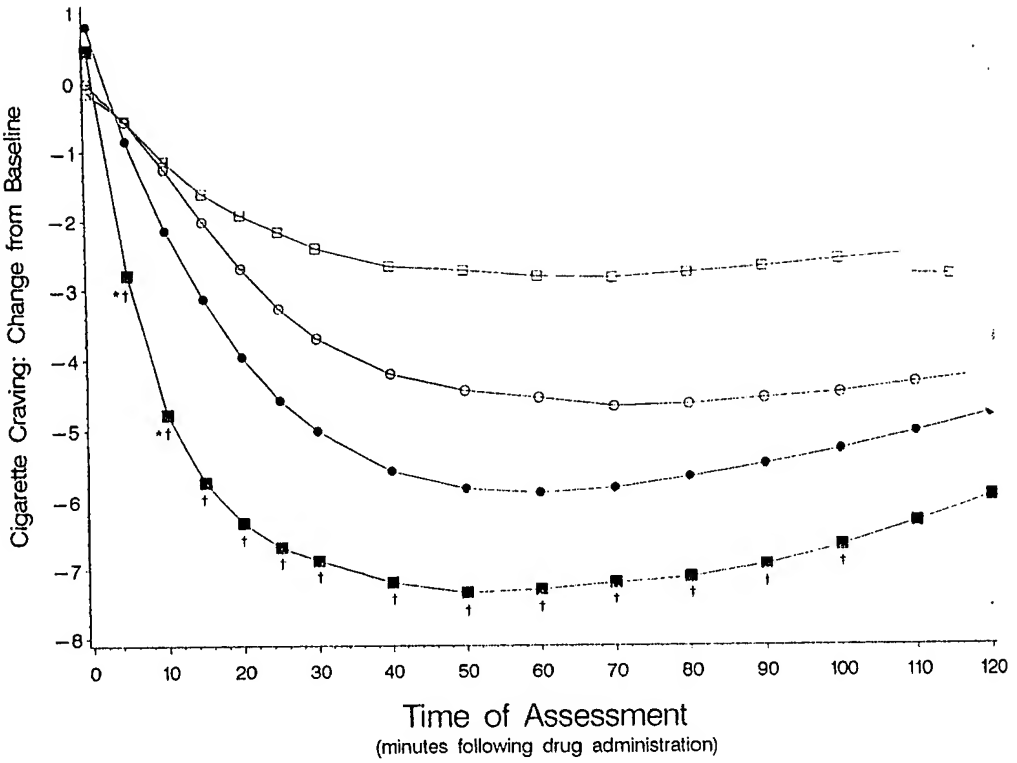

Fig. 4 Mean craving for a cigarette change from baseline in cumulative area under the curve, averaged across all three study sessions. Craving for a cigarette score is based on a scale from 1 (no craving) to 41 (extreme craving). A larger negative value represents a larger reduction in craving for a cigarette score. *$P < 0.05$ from two-sample t-test comparing active spray versus active gum. †$P < 0.05$ from two-sample t-test comparing active spray versus placebo spray. □ Placebo spray (n =16), ○ placebo gum (n = 15), ● 4 mg active gum (n = 31), ■ 1 mg active spray (n = 29)

reduction from baseline in nicotine withdrawal for active nicotine nasal spray was significantly greater than active nicotine gum at 5 min (-0.9 ± 1.5 versus -0.2 ± 1.0, $P = 0.012$). For the active nicotine nasal spray, the reduction in nicotine withdrawal was significantly greater than the placebo spray at times 5–60 min (all $P \leq 0.05$). No significant differences were detected between the active nicotine gum and the placebo gum with respect to the change in overall nicotine withdrawal at any time. The changes in overall nicotine withdrawal scores were not significantly correlated with serum nicotine levels.

Figure 4 shows the change from baseline in cigarette craving scores for the four groups. The AUC reduction from baseline in craving for a cigarette for active nicotine nasal spray was significantly greater than active nicotine gum at 5 min (-2.8 ± 3.9 versus -0.9 ± 2.6, $P = 0.026$) and 10 min (-4.8 ± 5.8 versus -2.2 ± 2.9, $P = 0.029$), respectively. For the active nicotine nasal spray group, the reduction in cigarette craving was significantly greater than the placebo spray group at times 5–100 min (all $P \leq 0.05$). No significant differences were detected between the active nicotine gum and the placebo gum with respect to cigarette craving at any time. Changes in craving for a cigarette scores during the first session were not found to be significantly correlated with serum nicotine levels.

The AUC reduction from baseline in cigarette withdrawal for the active nicotine nasal spray group (-2.0 ± 4.0) was significantly greater than the active nicotine gum group (-0.3 ± 2.3, $P = 0.039$) at 5 min and the placebo spray at 5, 10, and 15 min (all $P \leq 0.05$). No significant differences were detected between the active nicotine gum and either placebo group with respect to cigarette withdrawal at any time. Changes in cigarette withdrawal scores during the first session were not found to be significantly correlated with serum nicotine levels.

Discussion

To our knowledge, this is the first direct comparison of nicotine nasal spray and nicotine gum and their effect on nicotine withdrawal symptoms and nicotine blood levels achieved by a single dose of each. The findings show that a 1 mg dose of the nicotine nasal spray provides more immediate relief of craving for a cigarette than 4 mg nicotine gum, a difference which was detectable only at the first 10 min following administration. After this time period, the relief of craving was comparable between the two delivery systems. This indicates that the nicotine nasal spray has the greater potential for use in acute situations when more immediate relief for a cigarette craving is desired. This might be the case in more addicted smokers or in those who have previously relapsed because of the intensity of the nicotine craving. Though nicotine gum has been previously reported to relieve nicotine withdrawal symptoms (Cepeda-Benito 1993), we were unable to demonstrate that finding when using a single dose of 4 mg nicotine gum compared to placebo.

We used the 4 mg gum to give the greatest chance to show an active versus placebo effect while minimizing chances for an active gum versus spray difference. Given that the nicotine nasal spray dose was only one-half of the nicotine gum dose (the 4 mg gum, when used properly, will deliver approximately 2 mg nicotine) and the T_{max} for nicotine gum is longer than for the nicotine nasal spray, it was not surprising to find that the 4 mg nicotine gum dose produced higher median serum nicotine levels at 30 min. The T_{max} in previous nicotine nasal spray experiments after a single 1 mg dose was 11.5 min, and the C_{max} was 8.1 with a range of 2.5–13.3 (Johansson et al. 1991). We did not find a significant correlation between the venous nicotine levels and changes in nicotine withdrawal symptoms. We did not measure arterial nicotine levels which may have shown a correlation with nicotine withdrawal relief, since the arterial levels are higher than the venous levels, at least for the nicotine nasal spray (Gourlay and Benowitz 1997).

A potential application of our findings is the use of one of these two immediate acting forms of nicotine replacement therapy in conjunction with a slower delivery system such as nicotine patch therapy. When 2 mg nicotine gum was combined with nicotine patch therapy, there was better nicotine withdrawal relief and possibly better efficacy for smoking cessation than with either used alone (Fagerström et al. 1993; Kornitzer et al. 1995; Puska et al. 1995). Though there was no patch condition in our study, our findings suggest that if combination therapy were used with nicotine patch therapy, there would be more immediate relief of craving for a cigarette with nicotine nasal spray than with nicotine gum.

Strengths of this study are that it was conducted under carefully controlled, smoke-free conditions, the subjects were blinded, and there were large sample sizes for each arm. We also made multiple measures of nicotine withdrawal symptoms over three separate sessions, and there were multiple blood draws during the first session to obtain the serum nicotine levels.

Weaknesses included the fact that some subjects had detectable nicotine levels even after overnight abstinence, an observation made in other studies (Gourlay and Benowitz 1997). The lower detection limit of the nicotine assay that we used was 2.0 ng/ml. Thus, some of the levels that were reported as non-detectable could have been between 0.1 and 1.9 ng/ml. We also did not have available to us the true placebo nicotine nasal spray with the capsaicin pepper, but rather used a saline solution in a nasal spray bottle. Side effects to the capsaicin pepper spray could have a confounding effect on the perception of some of the withdrawal symptoms.

In conclusion, we have reported that a single 1 mg dose of nicotine nasal spray provides more immediate relief (within 5–10 min) of craving for a cigarette compared to a single dose of 4 mg nicotine gum. After 10 min, the craving relief was comparable between the two delivery systems. Thus in patients desiring more immediate relief of craving for a cigarette, the nicotine nasal spray would be preferred over the nicotine gum. This was despite there being no significant differences in serum venous nicotine levels between the active nasal spray and gum groups at 5 and 10 min after drug administration. Only at 30 and 120 min did the nicotine gum provide a higher serum venous nicotine level than the nicotine nasal spray. Finally, changes in nicotine withdrawal symptoms were not found to be correlated with serum venous nicotine levels.

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